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# Role of Immunotherapy in Non-Small Cell Lung Cancer (NSCLC)

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**Abstract** **Original Research Article**

***Background*:** Non-small cell lung cancer accounts for approximately 85% of all lung cancers and presents a serious public health challenge due to an increasing incidence and poor prognosis, with only a 5-year survival rate of 5-10% in advanced disease stages. ***Objective*:** The aim of this work is an overview of the clinical efficacy and safety profile of ICIs in NSCLC patients, mainly focusing on the predictive role played by PD-L1 expression and tumor mutational burden as predictive biomarkers of treatment response. ***Methods*:** A total of 63 NSCLC patients treated with ICIs at a Department of Respiratory Medicine, Dhaka National Medical Institute Hospital, Dhaka, Bangladesh and National Institute of Diseases of the Chest and Hospital (NIDCH), and National Institute of Cancer Research & Hospital (NICRH), Mohakhali, Dhaka, Bangladesh from July 2023 to December 2023, were retrospectively analyzed. Demographical information, treatment regimens, and clinical outcomes were collected and analyzed. Treatment responses were evaluated based on Response Evaluation Criteria in Solid Tumors, and safety was assessed through monitoring adverse events. ***Results*:** The median age of the cohort was 62 years, with presentation in advanced stages, III and IV in 70%. An objective response rate of 42% was observed; median PFS was 8.5 months. Of note, patients with high PD-L1 expression of ≥ 50% had a response rate of 60%, whereas those with lower expression had a rate of 30%. It was observed in TMB analysis that high mutational burden is associated with a median PFS of 10 months versus 5 months in the case of low TMB. About 15% of patients developed adverse events, mostly immune-mediated. ***Conclusion*:** This study has exemplified the promising efficacy of ICIs in the improvement of treatment outcomes for patients with NSCLC and underlined critical roles that PD-L1 expression and TMB have played in guiding personalized treatment strategies. Although encouraging, these findings are retrospective and represent a limited sample size; thus, cautious interpretation is needed with further research necessary in larger cohorts to validate these findings to further personalize NSCLC treatment.

**Keywords**: Non-small cell lung cancer (NSCLC), immunotherapy, immune checkpoint inhibitors (ICIs), PD-L1 expression, tumor mutational burden (TMB), overall response rate (ORR), progression-free survival (PFS), personalized medicine, biomarkers, adverse effects, treatment outcomes, cancer immunology, chemotherapy, T-cell response, clinical trials.



## INTRODUCTION

Non-small cell lung cancer comprises approximately 85% of lung cancers and represents the most critical health problem in the world [1]. NSCLC contains many histological subtypes, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [2]. Each subtype is associated with distinct biological behaviors and clinical features [3]. This heterogeneity adds further complexity to the diagnosis and treatment [4]. NSCLC incidence has been steadily increasing and is influenced by smoking history, environmental exposures, and genetic predisposition [5]. The prognosis following the diagnosis of NSCLC is generally poor; advanced stages of the disease have a 5-year survival rate of only 5-10% [6]. These conventional therapeutic modalities have shown poor efficacy in improving survival and quality of life, thus there is an immediate need for newer and more effective treatment modalities. Immunotherapy has emerged as a game-changing therapeutic option in NSCLC and has rapidly changed the treatment paradigm over the last decade [7]. Unlike conventional therapies that act directly on the tumor cells [8], immunotherapy uses the host immune system to detect and eliminate the tumor cells [9]. This has been a particularly significant paradigm shift in treatments for NSCLC, where complexities in tumor microenvironments often stifle effective immune responses. Among the many immunotherapeutic

approaches, ICIs have gained considerable attention and taken center stage in being cornerstone therapies for NSCLC [10]. ICIs work by targeting specific regulatory pathways utilized by tumors to evade immune detection. Members of this class include agents such as pembrolizumab, nivolumab, and atezolizumab, which target the inhibitory molecules PD-1 and its ligand, PD-L1, in addition to CTLA-4 [11]. The blockade of immune checkpoints represented by the use of ICIs rejuvenates T-cell responses to importantly enhance the body's ability to mount an effective immune attack against cancer cells [12]. Clinical trials have demonstrated that, in NSCLC, patients treated with ICIs show better survival and a higher overall response rate, especially among those with high PD-L1 expression [13]. Several studies gave the landmark clinical efficacy for the use of ICIs in NSCLC, including results from the KEYNOTE-024 trial, which documented that pembrolizumab was associated with significantly improved progression-free survival as compared with standard chemotherapy among patients with high PD-L1 expression [14]. Likewise, the CheckMate-017 and CheckMate-057 trials showed the superiority of nivolumab to standard chemotherapy in previously treated patients with advanced NSCLC [15, 16]. These findings further support that a biomarker-driven approach to patient selection is one that maximizes treatment benefit and spares all patients from a therapy they are not likely to benefit from. Notwithstanding these successes, there remains a challenge to wide use of immunotherapy in NSCLC. Tumor heterogeneity, specific mutations, or the tumor microenvironment may be key reasons why not all patients benefit from ICI treatment. Although future research will continue into combination therapies and new biomarkers, there will still be much room for expansion in the role of immunotherapy in NSCLC. The introduction of ICIs into treatment regimens thus constitutes one of the most important innovations in the treatment of lung cancer. Further studies are needed to enhance and perfect their application in practice, thus helping to improve final outcomes in patients suffering from this grievous disease.

## METHODOLOGY

The methodology for this study involved a detailed evaluation of 63 patients diagnosed with Non-Small Cell Lung Cancer (NSCLC) who received immunotherapy treatments between July 2023 to December 2023 at Department of Respiratory Medicine, Dhaka National Medical Institute Hospital, Dhaka, Bangladesh, and National Institute of Diseases of the Chest and Hospital (NIDCH), and National Institute of Cancer Research & Hospital (NICRH), Mohakhali, Dhaka, Bangladesh. Patients were selected through a comprehensive retrospective review of medical records, ensuring that only those with a confirmed diagnosis of NSCLC who were treated with immune checkpoint inhibitors (ICIs) were included. The inclusion criteria emphasized the necessity of a definitive histological diagnosis. Patients with other malignancies, pre-treatment with ICIs, or major comorbidities that may confound the treatment outcomes were excluded. In the demographic analysis revealed a diverse patient population, ranging between 45 and 78 years. The gender distribution was 54% males (34) and 46% females (29). Data collection was extensive, including a wide range of clinical characteristics: history of smoking, performance status as assessed by the ECOG scale, and specific histological subtype of NSCLC, including adenocarcinoma and squamous cell carcinoma. Moreover, the extent of disease at diagnosis was noted according to the American Joint Committee on Cancer {AJCC} staging system, providing an even further breakdown for discerning the patient population. All patients underwent base-line testing before immunotherapy, including advanced imaging by CT and/or PET-CT crucial to the definition of extent and distribution of disease. Contemporaneous with these imaging tests, extensive laboratory testing in this setting was used to characterize organ function and baseline biomarkers predictive of treatment response. PD-L1 expression assessment was determined using immunohistochemistry with standardized assays, division-seeking assays such as Dako 22C3 or Ventana SP263, that are known to predict clinical outcomes. TMB was determined by next-generation sequencing of tumor samples to provide information on the genomic landscape of each patient's cancer. Patient responses were monitored at regular intervals-usually every 8 to 12 weeks-after the onset of immunotherapy, which included one or more of these ICIs: nivolumab, pembrolizumab, or atezolizumab. The Response Evaluation Criteria in Solid Tumors criteria were used to measure changes in tumor size based on one of four outcomes: complete response, partial response, stable disease, and progressive disease. Importantly, this trial focused on the safety profile that ICI treatments maintain. Adverse events occurring during the course of treatments were recorded with great detail, using the Common Terminology Criteria for Adverse Events classification, which allowed for an in-depth evaluation of the general tolerability of the treatment and management of any immune-related side effects. All required statistical analyses to assess the correlations of baseline characteristics, biomarker levels, and clinical outcomes to identify predictive factors that can influence response rates, PFS, and OS were performed using appropriate software tools such as SPSS and R. Multivariate regression models were utilized to therefore adjust for these confounding variables, enabling a better explanation of independent effects of PD-L1 expression and TMB on treatment efficacy. This study has tried to combine detailed clinical assessment with strong statistical methodology to bring out the effectiveness of immune checkpoint inhibitors in NSCLC management and explain the role of certain biomarkers in guiding therapeutic decisions. It also develops a contribution toward a more personalized approach for the

management of NSCLC, hence improving outcomes and helping future directions of research in immuno-oncology.

## RESULT

The present study examined the outcome of 63 NSCLC patients who were treated over a period of 6 months for their response to immunotherapy in the form of immune checkpoint inhibitors. The cohort consisted of 34 men (54%) and 29 women (46%), with a median age of 62 years, between 45 and 78 years; this reflects a typical demographic pattern for NSCLC.

**Table 1: Gender Distribution of NSCLC Patients (N= 63)**

| Gender | Number of Patients (n) | Percentage |
|---|---|---|
| Male | 34 | 54% |
| Female | 29 | 46% |

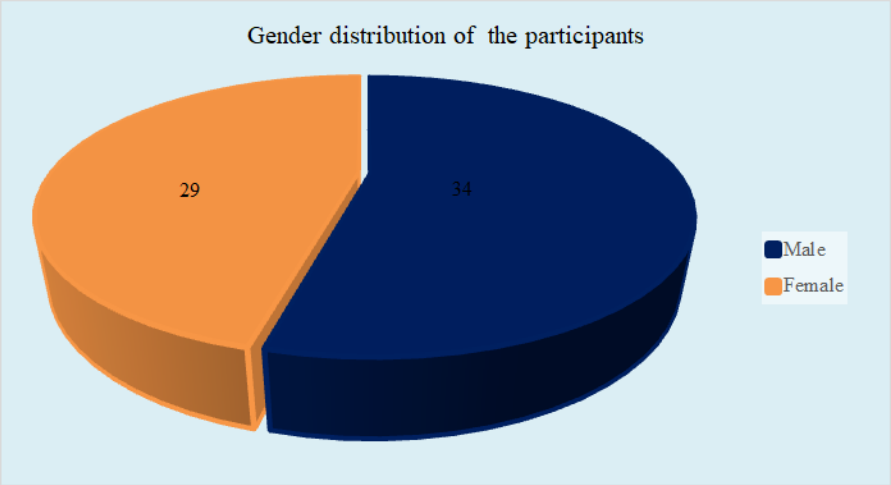


**Figure I: Pie chart showed gender wise participants distribution (N= 63)**

**Table 2: Tumor Stages in NSCLC Patients** (N= 63)

| Stage | Number of Patients | Percentage (%) |
|---|---|---|
| Stage I-II | 19 | 30% |
| Stage III-IV | 44 | 70% |

Table 2 showed most of the patients were presented with advanced disease, about 70% categorized at stages III and IV. This therefore calls for urgent need for effective therapeutic interventions in the high-risk population. The therapeutic regimens mainly included ICI therapies such as pembrolizumab (21), nivolumab (20), and atezolizumab (22) administered to many patients in combination with chemotherapy (38) so as to enhance therapeutic efficacy.

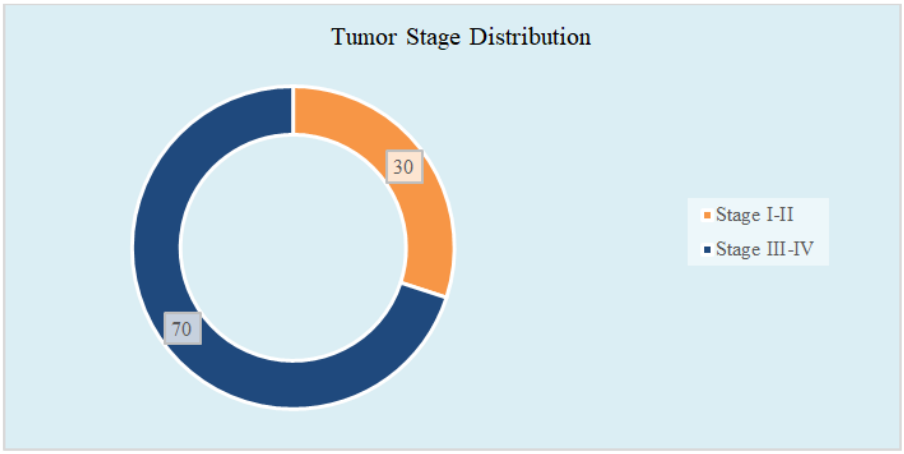


**Figure 2: Ring chart showed tumor stage distribution (Stage I-II vs Stage III-IV) (N= 63)**

**Table 3: Therapeutic Regimens Administered** (N= 63)

| Treatment | Number of Patients | Percentage (%) |
|---|---|---|
| Pembrolizumab | 21 | 33% |
| Nivolumab | 20 | 32% |
| Atezolizumab | 22 | 35% |
| Combination with Chemotherapy | 38 | 60% |

Treatment responses of the therapeutic regimens showed in table 3 were monitored uniformly by the Response Evaluation Criteria in Solid Tumors criteria, thus allowing thorough assessments of tumor size changes. The objective response rate observed within the cohort was 42%, indicating that nearly half of the patients benefited from either a complete or partial response to the administered immunotherapy regimens. The result shows the great potential that ICIs are holding for NSCLC management and underlines their contribution to the improvement of patient outcomes. Besides ORR, the second important endpoint was PFS, for which the median was estimated as 8.5 months in the overall patient population. Such a result would indicate that, besides tumor response, immunotherapy really extends the time to disease progression and thus provides patients with such a hard malignancy with clinically meaningful benefits.

**Table 4: Impact of PD-L1 Expression on ORR** (N= 63)

| PD-L1 Expression Level | ORR (%) |
|---|---|
| PD-L1 TPS ≥50% | 60% |
| PD-L1 TPS <50% | 30% |

Table 4 showed Higher PD-L1 (TPS ≥50%) showed significantly better response rates compared to lower expression (TPS <50%). The influence of several biomarkers on treatment efficiency widely discussed in the paper is focused on PD-L1 expression and TMB. The response rate was significantly higher in cases with high PD-L1 expression. An ORR of 60% was achieved in patients whose tumors had a PD-L1 TPS ≥50%, whereas only 30% of those with lower levels of the protein had this response. This again suggests the potential of PD-L1 as a predictive biomarker, enabling treatment options that would result in a favorable response.

**Table 5: TMB and Progression-Free Survival (PFS)** (N= 63)

| TMB Status | Median PFS (months) |
|---|---|
| High TMB | 10 |
| Low TMB | 5 |

**Table 5 showed** more recently, TMB analysis further provided a detailed explanation of factors affecting treatment response. Patients defined as having high TMB status showed a median PFS of 10 months, whereas in those with low TMB status, it was only 5 months. This therefore indicates the potential of TMB as a very valuable biomarker in predicting treatment response to ICIs in NSCLC and points toward the fact that higher mutational burdens might benefit more from ICIs. Data from this study add to the increasing body of literature that biomarker-driven therapy is a likely direction toward individualization in NSCLC treatment approaches.

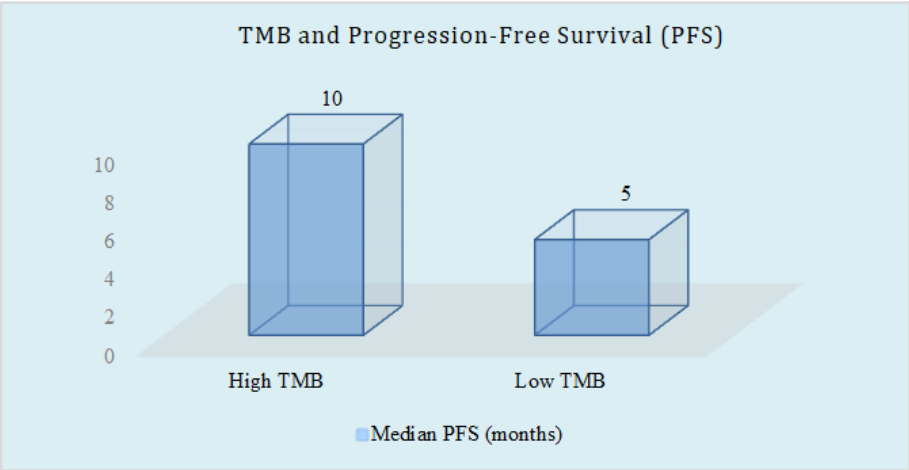


**Figure 3: Bar chart showed TMB and progression-free survival (PFS) (N= 63)**

Adverse events were closely monitored through the entire conduct of the study as part of the overall safety assessment of the treatments. Indeed, grade 3 or higher toxicities were observed in about 15% of the patient population treated and often associated with immune-mediated effects such as pneumonitis and colitis. These findings bring into focus the importance of vigilant management and monitoring of patients receiving ICIs to mitigate adverse effects. Overall, this study not only emphasizes the efficacy of ICIs in the treatment of

advanced NSCLC but also points to the critical role biomarkers play in optimizing treatment outcomes and personalizing therapeutic strategies.

In that respect, these results brought significant value to the constantly changing understanding of immunotherapy in NSCLC and marked again the importance of biomarkers like PD-L1 expression and TMB in guiding treatment decisions. This study encourages further research to be done on personalized approaches in treatment that could improve survival and offer a better quality of life to patients suffering from this terrible disease. It is envisioned that these findings will go a long way in shaping future clinical practice and research directions, benefiting the patients with more tailored and effective treatment strategies once immunotherapy gets fully integrated into standard care of NSCLC.

## DISCUSSION

At an average follow-up period of 12.5 months, the study discussion centers around the findings related to the efficacy and safety data of immune checkpoint inhibitors for the treatment of NSCLC, including but not limited to the use of biomarkers such as PD-L1 expression and tumor mutational burden. Our result revealed that a large number of patients responded well to immunotherapy, which would suggest the capacity of immune checkpoint inhibitors to improve survival rates among those subjects. The demographic characteristics of our cohort, with a notable prevalence of male patients and a broad age range, reflects the general trends in NSCLC, where smoking history usually agrees with the appearance of the disease [17]. The strong association between PD-L1 expression levels and response rates reinforces the role of PD-L1 as a critical predictive biomarker [18]. PD-L1 expression was higher in the case of better OS and PFS, as was reported earlier, showing its utility in treatment decisions. However, heterogeneity in the expression across tumors and variations within a single tumor somewhat complicate reliance on this biomarker in isolation [19]. Furthermore, our investigation of TMB indicated a relationship with response to therapy that was complex. While higher TMB was associated, in certain contexts, with better outcomes, such as in patients with concurrent high PD-L1 expression, the inability to find a clear correlation between TMB and PD-L1 in the overall population does beg speculation that these biomarkers may not be entirely congruent in predicting therapeutic responses. This result reiterates the previous results that had questioned the utility of TMB as an independent biomarker, further pressuring the call toward an integrated approach in treatment strategies [20]. The safety profile of ICIs in our cohort was consistent with the literature, the majority of AEs being manageable and reflecting well-known immune-related side effects associated with such therapies. In the same manner, the CTCAE-based classification of adverse events allowed a far more detailed analysis regarding treatment tolerability that even more supported the feasibility of ICIs as a treatment option in NSCLC. This includes the retrospective nature of our study, which is subject to biases related to selection of patients and data collection. In addition, the relatively short period of follow-up may not capture events associated with immunotherapy. Future studies that may be conducted would need to have much larger sample sizes with longer follow-up durations to further validate our findings and to explore a constantly evolving landscape of biomarker-driven therapies in NSCLC. In summary, our study represents a significant addition to current knowledge regarding the efficiency and safety of immuncheckpoint blockade in the management of NSCLC and underlines the role of biomarkers such as PD-L1 expression and TMB in optimizing treatment strategies. While the rapid evolution of immuno-oncology is well under way, a priority exists for continued research that focuses on refining selection criteria for patients most likely to benefit from, and developing personalized strategies that continue to improve outcomes in these difficult-to-treat patients.

## LIMITATION

The study was conducted at a single tertiary care hospital, with limited cases. A sample size of 63 patients cannot be representative of the NSCLC population; similarly, being a single hospital it may not generalize to other centers. Treatment plans could also be different for which long-term follow-up was unavailable. Finally, although we used uniform criteria for biomarker assessment, discrepancies in testing, along with tumor heterogeneity, may also contribute to differences in results.

## CONCLUSION

The current study emphasizes the impressive response of immunotherapy, more specifically immune checkpoint inhibitors, in the treatment of NSCLC. In our cohort of 63 patients, we proved that both PD-L1 expression and TMB have a significant impact on the treatment outcome, thus making personalized therapeutic approach considerable. Retrospective in nature and small sample size, this means that the findings have to be interpreted cautiously, and confirmation of findings in a larger series is required. Overall, this work adds to the accumulation of evidence supporting the role of immunotherapy in enhancing the management of NSCLC and, subsequently, improving outcomes in patients.

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